PATENT ABSTRACTS OF JAPAN

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(71)Applicant : W R GRACE & CO

(72)Inventor : NAKAO AKIKIMI
YOSHIOKA HIROSHI
MORI YUICHI

(54) DRUG CARRIER

(57)Abstract:

PURPOSE: To obtain a drug carrier capable of readily administering because of liquid at administration temperature and continuously releasing a medicine because of instantaneous gelation in vivo and in biological lumen and keeping medicinal concentration for a long time.

CONSTITUTION: This drug carrier comprises a polymer capable of gelling at lower temperature than body temperature and exhibiting water-soluble property at the gelation temperature, preferably a polymer obtained by binding (A) a temperature-sensitive polymer, e.g. poly(N-isopropylacrylamine-co-N- acryloyloxysuccinimide) to (B) a water-soluble polymer, e.g. polyethylene oxide aminated at both ends and having a plural number of A parts in the molecule. The drug carrier can carry out oral administration, injection, injection by catheter, etc., because the carrier has the above effect and can maximally exhibit pharmacodynamic effects and reduce adverse effects, because the carrier can increase release control of the medicine and biological bioavailability.

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CLAIMS

[Claim(s)]
[Claim 1]A drug carrier consisting of a high molecular compound in which it gels at a temperature lower than body temperature, and water solubility is shown at temperature below this gelation temperature.
[Claim 2]The drug carrier according to claim 1 with which two or more temperature sensitive high molecular compound portions which said high molecular compound is a high molecular compound in which a temperature sensitive high molecular compound which has LCST lower than body temperature, and a water soluble polymer compound are combined, and have this LCST exist in a monad.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application]This invention relates to the drug carrier which may emit a drug continuously within [in the living body or] a living body's lumen. In order to be able to prescribe a medicine for the patient easily at administration temperature since it is liquefied, and to gel in [in the living body or] a living body's lumen in more detail, it is related with drug Carrier who can emit a drug continuously.
[0002]
[Description of the Prior Art]In recent years, development of the drug delivery system (Drug Delivery System, DDS) which is a required medication method which suppresses side effects to the minimum by carrying out time supply and demonstrating drug effect to the maximum extent is actively performed to the affected part for which only a complement needs a drug. The in-plant system in the living body which composite-izes a drug to the matrix of various gestalten, detains in an organ, an organ, subcutaneous tissue, and a living body's lumen etc., and makes a drug gradual-release-ize as most typical example is developed.
[0003]By detaining directly the implant which composite-ized the anticancer agent to the polymer carrier in a cancer disease nest as an in-plant system in the living body, and carrying out self-sustaining discharge of the anticancer agent, what expected the remission of tumor reduction, the prolongation of life, and a cancer pain, etc. is developed, and much clinical application is performed about this. Immunostimulators, such as various hormone drugs, interferon, and interleukin, a narcotics antagonist, anesthetic, etc. are applied to this system besides the anticancer agent. The implant in the living body distributes the drug mainly by the physical means to the matrix of Polymer Division, and performs gradual release-ization by diffusing a drug from the inside of The Matrix. Since composite-izing of a drug and a matrix is easy, the range of an object drug has the advantage that it is large and inactivation of the pharmacological activity of the drug in a manufacturing process is hardly accepted.

[0004]By the way, in order to carry out clinical efficacy of these implant in the living body, the implant of shape according to an application site, such as a needle, the shape of a rod, film state, and a pellet type, must be laid underground by surgical operation etc. in the living body. The dosage forms with such an inescapable surgical operation are not desirable on [from a point of a patient's pain, an infectious disease, the remains of an operative scar, etc.] clinical efficacy.
[0005]Since the implant detained in the living body has various shape as mentioned above, the ** office of the operation of the drug emitted is easy to be carried out only to the portion which touches the implant, and the concentration-of-drug distribution by a focus part tends to become uneven.
[0006]As mentioned above, there are various serious problems in the conventional in-plant system in the living body, and the drug carrier with which administration is simple and it can moreover be satisfied of sustained-release [sufficient] is not yet provided.
[0007]
[Problem(s) to be Solved by the Invention]Then, this invention is easy to prescribe a medicine for the patient, and it aims at providing the drug carrier which can maintain concentration of drug in [in the living body or] a living body's lumen for a long time.
[0008]
[Means for Solving the Problem]The above-mentioned purpose can be gelled at a temperature lower than body temperature, and drug Carrier consisting of a high molecular compound in which water solubility is shown can attain it at temperature below this gelation temperature.
[0009]A high molecular compound used for a drug carrier of this invention may have the above-mentioned character, and as long as it is not harmful in in the living body, it may be what kind of substance. A thing desirable as this high molecular compound is the high molecular compound in which a temperature sensitive high molecular compound which has LCST, and a water soluble polymer compound were combined.
[0010]With a temperature sensitive high molecular compound which has LCST. A solubility temperature coefficient to water is a high molecular compound in which negative is shown, and a hydrate (oxoniumhydroxide) depending on a hydrogen bond of a high molecular compound and a water molecule which are generated at low temperature decomposes at an elevated temperature, and it has the feature which high molecular compounds condense by the drying sum, and precipitates. With LCST (Lower Critical Solution Temperature). Transition temperature of hydration of such a temperature sensitive high molecular compound and the drying sum is said (for example, J. Macromol of Haskins and others (M. Haskins), Sci.-Chem., A2 (8), and 1441 (1986) reference). That is, although a temperature sensitive high molecular compound of this invention dissolves in water by hydrophilic nature at temperature below LCST, at temperature more than LCST, it becomes hydrophobicity, and precipitates, and this change is reversible. In this invention, it is required for LCST of the above-mentioned temperature sensitive high molecular compound to be a temperature lower than body temperature.

[0011]As a temperature sensitive high molecular compound used for this invention, a poly N substitution acrylamide derivative, poly N substitution meta-acrylamide derivatives and these copolymers, polyvinyl methyl ether, a polyvinyl alcohol partial acetylation thing, etc. are mentioned. LCST enumerates desirable temperature sensitive high molecular compounds below at low order.

[0012]Polly N-acryloyl piperidine;. Polly N-n-propyl meta-acrylamide;. Polly N-isopropylacrylamide;. Polly N,N-diethylacrylamide;. Polly N-isopropyl meta-acrylamide;. Polly N-cyclopropylacrylamide; -- Polly N-acryloyl pyrrolidine; -- Polly N,N-ethyl methylacrylamide; -- Polly N-cyclopropyl meta-acrylamide; -- a high molecular compound of the Polly N-ethylacrylamide above, It may polymerize or copolymerization of the single monomer may be carried out to other monomers. Hydrophobic either a hydrophilic monomer or a monomer can be used for a monomer which carries out copolymerization. Generally, if copolymerization is carried out to a hydrophilic monomer, LCST of output will go up, and if copolymerization is carried out to a hydrophobic monomer, LCST of output will descend. Therefore, a high molecular compound which has desired LCST can be obtained also by choosing these suitably.

[0013]As a hydrophilic monomer, N-vinyl pyrrolidone, vinylpyridine, acrylamide, Meta-acrylamide, N-methylacrylamide, hydroxyethyl methacrylate, Hydroxyethyl acrylate, hydroxymethyl methacrylate, Acrylic acid and methacrylic acid which have hydroxymethyl acrylate and an acidic group, and those salts, Although N [which has basicity such as vinylsulfonic acid and styrene sulfonic acid,], N-dimethylaminoethyl methacrylate, N, and N-diethylamino ethyl methacrylate, N,N-dimethylaminopropyl acrylamide, those salts, etc. are mentioned, It is not limited to these.

[0014]On the other hand as a hydrophobic monomer, ethyl acrylate, methyl methacrylate, Although N substituted alkyl meta-acrylamide derivatives, such as acrylate derivatives, such as glycidyl methacrylate, and a methacrylate derivative, and N-n-butyl meta-acrylamide, VCM/PVC, acrylonitrile, styrene, vinyl acetate, etc. are mentioned, It is not limited to these.

[0015]On the other hand, a water soluble polymer compound used for this invention, If it is a high molecular compound meltable to water, there will be no restriction in particular, and For example, polyethylene oxide, Polyvinyl alcohol, Polly N-vinyl pyrrolidone, polyvinyl pyridine, Polyacrylamide, poly meta acrylamide, Polly N-methylacrylamide, Polyhydroxyethyl methacrylate, polyhydroxy ethyl acrylate, A polyhydroxy methylmetaacrylate, polyhydroxy methyl acrylate, Polyacrylic acid, polymethacrylic acid, polyvinyl sulfonic acid, polystyrene sulfonate, and those salts, Polly N, N-dimethylaminoethyl methacrylate, Polly N, N-diethylamino ethyl methacrylate, Polly N,N-dimethylaminopropyl acrylamide, those salts, etc. are mentioned.

[0016]A polymerization nature functional group can be introduced into one of high molecular compounds, and combination with a temperature sensitive high molecular compound and a water soluble polymer compound which have LCST can be performed by carrying out copolymerization of the monomer which gives a high molecular compound of another side. For example, acrylic acid chloride is made to react to a both-ends hydroxyl group of polyethylene oxide which is a

water soluble polymer compound, By carrying out copolymerization of a monomer which gives a temperature sensitive high molecular compound which has LCST after introducing a polymerization nature functional group and an acrylic group, for example, the N-isopropylacrylamide, Combination of a temperature sensitive high molecular compound and a water soluble polymer compound which have LCST at about 30 ** can be obtained. A connective of a temperature sensitive high molecular compound and a water soluble polymer compound which have LCST is obtained also by block copolymerization of a monomer which gives a temperature sensitive high molecular compound, and a monomer which gives a water soluble polymer compound. A labile functional group is beforehand introduced into both, and combination with a temperature sensitive high molecular compound and a water soluble polymer compound which have LCST can be performed also by combining both by a chemical reaction. It is necessary to introduce two or more labile functional groups into a water soluble polymer compound at this time. For example, a temperature sensitive high molecular compound which introduced a basis which reacts to the 1st class amine easily by carrying out copolymerization of the N-acryloxy succinimide to N-isopropylacrylamide is compounded, Combination of a temperature sensitive high molecular compound and a water soluble polymer compound which have LCST at about 30 ** by the reaction of polyethylene oxide which is a water soluble polymer compound which has the 1st class amino group in this and both ends can be obtained.

[0017]At temperature below LCST of a temperature sensitive high molecular compound, since both a temperature sensitive high molecular compound portion and a water soluble polymer compound portion are water solubility, a connective of a temperature sensitive high molecular compound and a water soluble polymer compound dissolves in water thoroughly. However, since a temperature sensitive high molecular compound portion will become hydrophobicity if temperature of this solution is warmed to temperature more than LCST of a temperature sensitive high molecular compound, it meets between separate molecules by a hydrophobic interaction. On the other hand, since a water soluble polymer compound portion is water solubility also in this time, a connective generates hydro-gel with a three-dimensional network which made a hydrophobic meeting part between temperature sensitive high molecular compound portions a point constructing a bridge in underwater. Since a connective has such character, drug Carrier of this invention can confine a drug in an inside of gel in in the living body like the after-mentioned. At this time, since a water soluble polymer compound portion has too strong hydrophobic binding of temperature sensitive high molecular compound portions, a drug carrier precipitates and insolubilizes it, and it is serving to prevent a drug and this drug carrier dissociating thoroughly. If temperature of a gelled connective is again cooled to temperature below LCST of a temperature sensitive high molecular compound, a temperature sensitive high molecular compound portion will serve as water solubility, a point by hydrophobic meeting constructing a bridge will be released, and hydro-gel structure will disappear. For this reason, a connective serves as again perfect solution.

[0018]Drug Carrier of this invention can composite-ize with various drugs. As the composite-ized method, uniform solution of a drug carrier of this invention is produced at temperature below LCST, and a method of mixing with a desired drug is most generally used. While this composite-ized method is the simplest, it has the advantage that inactivation of the pharmacological activity of a drug is hardly accepted by a compound process. It is also possible to composite-ize simultaneously several drugs with which drug effect differed to a drug carrier of this invention.
[0019]Drug Carrier of a drug and composite-ized this invention can prescribe a medicine for the patient by pouring in or injecting mixed liquor of drug Carrier of a drug and this invention which were uniformly mixed at temperature below LCST into [in the living body or] a living body's lumen. Thus, a point which can be prescribed for the patient by a simple method is the important feature of this invention. After a medicine is prescribed for the patient into [in the living body or] a living body's lumen etc., shortly after becoming the temperature (body temperature) more than LCST of a temperature sensitive high molecular compound, a drug carrier of this invention is gelled and confines a drug in an inside of gel. For this reason, a drug inside gel is gradual-release-ized by diffusion phenomenon at the same time the retentivity of a drug in [in the living body or] a living body's lumen improves remarkably.
[0020]As for after pouring, moreover, since a drug carrier of this invention is a fluid at the time of administration, it can pour in, even if it does not perform a surgical operation etc. unlike the conventional implant in the living body, and it is possible to make a drug reach to management's all the corners. Unlike the conventional implant material in the living body, gel within [in the living body or] a living body's lumen is flexible, and a mechanical damage done to a body tissue and an organ is reduced remarkably.
[0021]
[Example]
(1) Poly (N-isopropylacrylamide -**- N-acryloxy succinimide) synthetic N-isopropylacrylamide 10.2g as a temperature sensitive high molecular compound, 0.135 g of N,N'-azobis yne butyronitrile was added to 400 ml of chloroform after the dissolution and a nitrogen purge, and 1.71 g of N-acryloxy succinimides were polymerized at 60 ** for 6 hours. It reprecipitated in diethylether after concentration. It condensed, and vacuum drying was carried out and 8.8 g of poly (N-isopropylacrylamide -**- N-acryloxy succinimide) was obtained.
(2) This poly (N-isopropylacrylamide -**- N-acryloxy succinimide) and 1.0 g of joint poly (N-isopropylacrylamide -**- N-acryloxy succinimide) of the both-ends amination polyethylene oxide as a water soluble polymer compound, 0.5 g of both-ends amination polyethylene oxide (molecular weight 6,000: made by Kawaken Fine Chemicals Co., Ltd.) was dissolved in 100 ml of chloroform, and it was made to react at 50 ** for 3 hours. To the room temperature, 0.1 g of isopropylamine was added after cooling, and it was neglected for 1 hour. It was made to precipitate in diethylether after concentration. It condensed, and vacuum drying was carried out and the drug carrier of 1.5-g this invention was obtained.

[0022]This drug carrier 0.5g was dissolved in 10 ml of distilled water under ice-cooling. When this solution was warmed gradually, mobility was lost and gelled above about 30 **. When this gel was cooled, mobility was regained below about 30 ** and it returned to solution again. This change was observed repeatedly reversibly.

[0023](3) 5-fluorouracil which has pyrimidine metabolism ****** which are this drug carrier and an anticancer agent. After dissolving this drug Carrier 0.2g at ordinary temperature into 1-ml physiological sodium chloride solution in the glass test tubes (inside diameter: 7 mm) whose composite-ized capacity of (abbreviating to 5-FU hereafter) is about 10 ml, After adding about 1-mg 5-FU (Harmony Fermentation) into this solution and making it dissolve thoroughly by shake, moved the test tube containing this solution to about 37 ** organ bath, it was made to settle for 5 minutes, and the gel containing 5-FU was made to form. Next, in order to simulate discharge of 5-FU from the gel containing 5-FU in the living body, About 5 ml of blood serums of **** beforehand warmed by 37 ** were added into the test tube held at 37 **, it quantified by the method of describing below 5-FU which shifts into a blood serum under shake, and the amount of 5-FU(s) which remains in this gel was presumed.

[0024]After adding 0.1 ml of perchloric acid 60% into 1 ml of blood serums extracted for every time, shaking for 2 minutes into them and carrying out high-speed centrifugality during 10 minutes at 12000 rpm, 0.2 ml of upper layers were extracted, 0.2 ml of ethyl acetate was added, and it centrifuged for 10 minutes at 3000 rpm. Under [a fixed quantity / high performance chromatography / (HPLC) / FU / 5-/ it extracts 20-60micro of lower layers I and]. The calibration curve of HPLC dissolved 5-FU (Harmony Fermentation) into the known amount and the blood serum, and produced it by the same method as the above. The Shimazu high-performance-chromatography device performed measurement of HPLC as a stationary phase, using the phosphoric acid 1 sodium solution of 0.02M as strongly acidic cation exchange resin (Shimadzu, and 4 mm[in inside diameter] x15 cm in length), and a mobile phase.

[0025]As a result of measuring the survival rate of 5-FU in gel by the above-mentioned method, the period until survival of 5-FU in gel becomes 50% of the first stage was about 25 hours.

[0026]After prescribing 5-FU for the patient for the residual action of 5-FU in a living body into the vein of ****, The result examined by measuring the survivability of 5-FU in a blood serum or a body tissue by HPLC, In the blood serum, a survival rate falls to about 50% in 10 to 20 minutes, a survival rate falls to 50% in 20 to 30 minutes also all over an organization, and producing disappearance in the living body of 5-FU dramatically for a short period of time is reported (Ikuo Katsumata, the odontology 70 (5), 869, 1983).

[0027]Therefore, it is possible by using the gel of this invention to extend remarkably the holding time of 5-FU in the inside of a living body.

[0028]

[Effect of the Invention]Since the drug carrier of this invention is a fluid at administration temperature, pouring by taking orally, injection, a catheter, etc., etc. are easy for it. And in order to

gel in an instant in the living body within a living body's lumen, the discharging control of a drug and extent of bioavailability can be increased. For this reason, maintenance of continuous effective concentration is possible, and drug effect can be demonstrated to the maximum extent, and also mitigation of side effects can also be performed.

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TECHNICAL FIELD

[Industrial Application]This invention relates to the drug carrier which may emit a drug continuously within [in the living body or] a living body's lumen. In order to be able to prescribe a medicine for the patient easily at administration temperature since it is liquefied, and to gel in [in the living body or] a living body's lumen in more detail, it is related with drug Carrier who can emit a drug continuously.

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PRIOR ART

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[0003]By detaining directly the implant which composite-ized the anticancer agent to the polymer carrier in a cancer disease nest as an in-plant system in the living body, and carrying out self-sustaining discharge of the anticancer agent, what expected the remission of tumor reduction, the prolongation of life, and a cancer pain, etc. is developed, and much clinical application is performed about this. Immunostimulators, such as various hormone drugs, interferon, and interleukin, a narcotics antagonist, anesthetic, etc. are applied to this system besides the anticancer agent. The implant in the living body distributes the drug mainly by the physical means to the matrix of Polymer Division, and performs gradual release-ization by diffusing a drug from the inside of The Matrix. Since composite-izing of a drug and a matrix is easy, the range of an object drug has the advantage that it is large and inactivation of the pharmacological activity of the drug in a manufacturing process is hardly accepted.
[0004]By the way, in order to carry out clinical efficacy of these implant in the living body, the implant of shape according to an application site, such as a needle, the shape of a rod, film state, and a pellet type, must be laid underground by surgical operation etc. in the living body. The dosage forms with such an inescapable surgical operation are not desirable on [from a point of a patient's pain, an infectious disease, the remains of an operative scar, etc.] clinical efficacy.
[0005]Since the implant detained in the living body has various shape as mentioned above, the ** office of the operation of the drug emitted is easy to be carried out only to the portion which touches the implant, and the concentration-of-drug distribution by a focus part tends to become

uneven.

[0006]As mentioned above, there are various serious problems in the conventional in-plant system in the living body, and the drug carrier with which administration is simple and it can moreover be satisfied of sustained-release [sufficient] is not yet provided.

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EFFECT OF THE INVENTION

[Effect of the Invention]Since the drug carrier of this invention is a fluid at administration temperature, pouring by taking orally, injection, a catheter, etc., etc. are easy for it. And in order to gel in an instant in the living body within a living body's lumen, the discharging control of a drug and extent of bioavailability can be increased. For this reason, maintenance of continuous effective concentration is possible, and drug effect can be demonstrated to the maximum extent, and also mitigation of side effects can also be performed.

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TECHNICAL PROBLEM

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MEANS

[Means for Solving the Problem]The above-mentioned purpose can be gelled at a temperature lower than body temperature, and drug Carrier consisting of a high molecular compound in which water solubility is shown can attain it at temperature below this gelation temperature.
[0009]A high molecular compound used for a drug carrier of this invention may have the above-mentioned character, and as long as it is not harmful in in the living body, it may be what kind of substance. A thing desirable as this high molecular compound is the high molecular compound in which a temperature sensitive high molecular compound which has LCST, and a water soluble polymer compound were combined.
[0010]With a temperature sensitive high molecular compound which has LCST. A solubility temperature coefficient to water is a high molecular compound in which negative is shown, and a hydrate (oxoniumhydroxide) depending on a hydrogen bond of a high molecular compound and a water molecule which are generated at low temperature decomposes at an elevated temperature, and it has the feature which high molecular compounds condense by the drying sum, and precipitates. With LCST (Lower Critical Solution Temperature). Transition temperature of hydration of such a temperature sensitive high molecular compound and the drying sum is said (for example, J. Macromol of Haskins and others (M. Haskins), Sci.-Chem., A2 (8), and 1441 (1986) reference). That is, although a temperature sensitive high molecular compound of this invention dissolves in water by hydrophilic nature at temperature below LCST, at temperature more than LCST, it becomes hydrophobicity, and precipitates, and this change is reversible. In this invention, it is required for LCST of the above-mentioned temperature sensitive high molecular compound to be a temperature lower than body temperature.
[0011]As a temperature sensitive high molecular compound used for this invention, a poly N substitution acrylamide derivative, poly N substitution meta-acrylamide derivatives and these copolymers, polyvinyl methyl ether, a polyvinyl alcohol partial acetylation thing, etc. are mentioned. LCST enumerates desirable temperature sensitive high molecular compounds below at low order.

[0012]Polly N-acryloyl piperidine;. Polly N-n-propyl meta-acrylamide;. Polly N-isopropylacrylamide;. Polly N,N-diethylacrylamide;. Polly N-isopropyl meta-acrylamide;. Polly N-cyclopropylacrylamide; -- Polly N-acryloyl pyrrolidine; -- Polly N,N-ethyl methylacrylamide; -- Polly N-cyclopropyl meta-acrylamide; -- a high molecular compound of the Polly N-ethylacrylamide above, It may polymerize or copolymerization of the single monomer may be carried out to other monomers. Hydrophobic either a hydrophilic monomer or a monomer can be used for a monomer which carries out copolymerization. Generally, if copolymerization is carried out to a hydrophilic monomer, LCST of output will go up, and if copolymerization is carried out to a hydrophobic monomer, LCST of output will descend. Therefore, a high molecular compound which has desired LCST can be obtained also by choosing these suitably.

[0013]As a hydrophilic monomer, N-vinyl pyrrolidone, vinylpyridine, acrylamide, Meta-acrylamide, N-methylacrylamide, hydroxyethyl methacrylate, Hydroxyethyl acrylate, hydroxymethyl methacrylate, Acrylic acid and methacrylic acid which have hydroxymethyl acrylate and an acidic group, and those salts, Although N [which has basicity such as vinylsulfonic acid and styrene sulfonic acid,], N-dimethylaminoethyl methacrylate, N, and N-diethylamino ethyl methacrylate, N,N-dimethylaminopropyl acrylamide, those salts, etc. are mentioned, It is not limited to these.

[0014]On the other hand as a hydrophobic monomer, ethyl acrylate, methyl methacrylate, Although N substituted alkyl meta-acrylamide derivatives, such as acrylate derivatives, such as glycidyl methacrylate, and a methacrylate derivative, and N-n-butyl meta-acrylamide, VCM/PVC, acrylonitrile, styrene, vinyl acetate, etc. are mentioned, It is not limited to these.

[0015]On the other hand, a water soluble polymer compound used for this invention, If it is a high molecular compound meltable to water, there will be no restriction in particular, and For example, polyethylene oxide, Polyvinyl alcohol, Polly N-vinyl pyrrolidone, polyvinyl pyridine, Polyacrylamide, poly meta acrylamide, Polly N-methylacrylamide, Polyhydroxyethyl methacrylate, polyhydroxy ethyl acrylate, A polyhydroxy methylmetaacrylate, polyhydroxy methyl acrylate, Polyacrylic acid, polymethacrylic acid, polyvinyl sulfonic acid, polystyrene sulfonate, and those salts, Polly N, N-dimethylaminoethyl methacrylate, Polly N, N-diethylamino ethyl methacrylate, Polly N,N-dimethylaminopropyl acrylamide, those salts, etc. are mentioned.

[0016]A polymerization nature functional group can be introduced into one of high molecular compounds, and combination with a temperature sensitive high molecular compound and a water soluble polymer compound which have LCST can be performed by carrying out copolymerization of the monomer which gives a high molecular compound of another side. For example, acrylic acid chloride is made to react to a both-ends hydroxyl group of polyethylene oxide which is a water soluble polymer compound, By carrying out copolymerization of a monomer which gives a temperature sensitive high molecular compound which has LCST after introducing a polymerization nature functional group and an acrylic group, for example, the N-isopropylacrylamide, Combination of a temperature sensitive high molecular compound and a water soluble polymer compound which have LCST at about 30 ** can be obtained. A connective

of a temperature sensitive high molecular compound and a water soluble polymer compound which have LCST is obtained also by block copolymerization of a monomer which gives a temperature sensitive high molecular compound, and a monomer which gives a water soluble polymer compound. A labile functional group is beforehand introduced into both, and combination with a temperature sensitive high molecular compound and a water soluble polymer compound which have LCST can be performed also by combining both by a chemical reaction. It is necessary to introduce two or more labile functional groups into a water soluble polymer compound at this time. For example, a temperature sensitive high molecular compound which introduced a basis which reacts to the 1st class amine easily by carrying out copolymerization of the N-acryloxy succinimide to N-isopropylacrylamide is compounded, Combination of a temperature sensitive high molecular compound and a water soluble polymer compound which have LCST at about 30 ** by the reaction of polyethylene oxide which is a water soluble polymer compound which has the 1st class amino group in this and both ends can be obtained.

[0017]At temperature below LCST of a temperature sensitive high molecular compound, since both a temperature sensitive high molecular compound portion and a water soluble polymer compound portion are water solubility, a connective of a temperature sensitive high molecular compound and a water soluble polymer compound dissolves in water thoroughly. However, since a temperature sensitive high molecular compound portion will become hydrophobicity if temperature of this solution is warmed to temperature more than LCST of a temperature sensitive high molecular compound, it meets between separate molecules by a hydrophobic interaction. On the other hand, since a water soluble polymer compound portion is water solubility also in this time, a connective generates hydro-gel with a three-dimensional network which made a hydrophobic meeting part between temperature sensitive high molecular compound portions a point constructing a bridge in underwater. Since a connective has such character, drug Carrier of this invention can confine a drug in an inside of gel in in the living body like the after-mentioned. At this time, since a water soluble polymer compound portion has too strong hydrophobic binding of temperature sensitive high molecular compound portions, a drug carrier precipitates and insolubilizes it, and it is serving to prevent a drug and this drug carrier dissociating thoroughly. If temperature of a gelled connective is again cooled to temperature below LCST of a temperature sensitive high molecular compound, a temperature sensitive high molecular compound portion will serve as water solubility, a point by hydrophobic meeting constructing a bridge will be released, and hydro-gel structure will disappear. For this reason, a connective serves as again perfect solution.

[0018]Drug Carrier of this invention can composite-ize with various drugs. As the composite-ized method, uniform solution of a drug carrier of this invention is produced at temperature below LCST, and a method of mixing with a desired drug is most generally used. While this composite-ized method is the simplest, it has the advantage that inactivation of the pharmacological activity of a drug is hardly accepted by a compound process. It is also possible to composite-ize

simultaneously several drugs with which drug effect differed to a drug carrier of this invention.
[0019]Drug Carrier of a drug and composite-ized this invention can prescribe a medicine for the patient by pouring in or injecting mixed liquor of drug Carrier of a drug and this invention which were uniformly mixed at temperature below LCST into [in the living body or] a living body's lumen. Thus, a point which can be prescribed for the patient by a simple method is the important feature of this invention. After a medicine is prescribed for the patient into [in the living body or] a living body's lumen etc., shortly after becoming the temperature (body temperature) more than LCST of a temperature sensitive high molecular compound, a drug carrier of this invention is gelled and confines a drug in an inside of gel. For this reason, a drug inside gel is gradual-release-ized by diffusion phenomenon at the same time the retentivity of a drug in [in the living body or] a living body's lumen improves remarkably.
[0020]As for after pouring, moreover, since a drug carrier of this invention is a fluid at the time of administration, it can pour in, even if it does not perform a surgical operation etc. unlike the conventional implant in the living body, and it is possible to make a drug reach to management's all the corners. Unlike the conventional implant material in the living body, gel within [in the living body or] a living body's lumen is flexible, and a mechanical damage done to a body tissue and an organ is reduced remarkably.

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EXAMPLE

[Example]
(1) Poly (N-isopropylacrylamide -**- N-acryloxy succinimide) synthetic N-isopropylacrylamide 10.2g as a temperature sensitive high molecular compound, 0.135 g of N,N'-azobis yne butyronitrile was added to 400 ml of chloroform after the dissolution and a nitrogen purge, and 1.71 g of N-acryloxy succinimides were polymerized at 60 ** for 6 hours. It reprecipitated in diethylether after concentration. It condensed, and vacuum drying was carried out and 8.8 g of poly (N-isopropylacrylamide -**- N-acryloxy succinimide) was obtained.
(2) This poly (N-isopropylacrylamide -**- N-acryloxy succinimide) and 1.0 g of joint poly (N-isopropylacrylamide -**- N-acryloxy succinimide) of the both-ends amination polyethylene oxide as a water soluble polymer compound, 0.5 g of both-ends amination polyethylene oxide (molecular weight 6,000: made by Kawaken Fine Chemicals Co., Ltd.) was dissolved in 100 ml of chloroform, and it was made to react at 50 ** for 3 hours. To the room temperature, 0.1 g of isopropylamine was added after cooling, and it was neglected for 1 hour. It was made to precipitate in diethylether after concentration. It condensed, and vacuum drying was carried out and the drug carrier of 1.5-g this invention was obtained.
[0022]This drug carrier 0.5g was dissolved in 10 ml of distilled water under ice-cooling. When this solution was warmed gradually, mobility was lost and gelled above about 30 **. When this gel was cooled, mobility was regained below about 30 ** and it returned to solution again. This change was observed repeatedly reversibly.
[0023](3) 5-fluorouracil which has pyrimidine metabolism ****** which are this drug carrier and an anticancer agent. After dissolving this drug Carrier 0.2g at ordinary temperature into 1-ml physiological sodium chloride solution in the glass test tubes (inside diameter: 7 mm) whose composite-ized capacity of (abbreviating to 5-FU hereafter) is about 10 ml, After adding about 1-mg 5-FU (Harmony Fermentation) into this solution and making it dissolve thoroughly by shake, moved the test tube containing this solution to about 37 ** organ bath, it was made to settle for 5 minutes, and the gel containing 5-FU was made to form. Next, in order to simulate discharge of 5-

FU from the gel containing 5-FU in the living body, About 5 ml of blood serums of **** beforehand warmed by 37 ** were added into the test tube held at 37 **, it quantified by the method of describing below 5-FU which shifts into a blood serum under shake, and the amount of 5-FU(s) which remains in this gel was presumed.

[0024]After adding 0.1 ml of perchloric acid 60% into 1 ml of blood serums extracted for every time, shaking for 2 minutes into them and carrying out high-speed centrifugality during 10 minutes at 12000 rpm, 0.2 ml of upper layers were extracted, 0.2 ml of ethyl acetate was added, and it centrifuged for 10 minutes at 3000 rpm. Under [a fixed quantity / high performance chromatography / (HPLC) / FU / 5-/ it extracts 20-60micro of lower layers I and]. The calibration curve of HPLC dissolved 5-FU (Harmony Fermentation) into the known amount and the blood serum, and produced it by the same method as the above. The Shimazu high-performance-chromatography device performed measurement of HPLC as a stationary phase, using the phosphoric acid 1 sodium solution of 0.02M as strongly acidic cation exchange resin (Shimadzu, and 4 mm[in inside diameter] x15 cm in length), and a mobile phase.

[0025]As a result of measuring the survival rate of 5-FU in gel by the above-mentioned method, the period until survival of 5-FU in gel becomes 50% of the first stage was about 25 hours.

[0026]After prescribing 5-FU for the patient for the residual action of 5-FU in a living body into the vein of ****, The result examined by measuring the survivability of 5-FU in a blood serum or a body tissue by HPLC, In the blood serum, a survival rate falls to about 50% in 10 to 20 minutes, a survival rate falls to 50% in 20 to 30 minutes also all over an organization, and producing disappearance in the living body of 5-FU dramatically for a short period of time is reported (Ikuo Katsumata, the odontology 70 (5), 869, 1983).

[0027]Therefore, it is possible by using the gel of this invention to extend remarkably the holding time of 5-FU in the inside of a living body.

[Translation done.]